

FEMALE SEXUAL FUNCTION

## Treatments for Persistent Genital Arousal Disorder in Women: A Scoping Review



María Martín-Vivar, PhD,<sup>1,2</sup> Alejandro Villena-Moya, MSc,<sup>1</sup> Gemma Mestre-Bach, PhD,<sup>3</sup> Felipe Hurtado-Murillo, PhD,<sup>4</sup> and Carlos Chiclana-Actis, MD, PhD<sup>1,3,5</sup>

### ABSTRACT

**Background:** Persistent genital arousal disorder (PGAD) is characterized by elevated discomfort associated with persistent genital arousal in the absence of sexual desire.

**Aim:** To perform a scoping review of the proposed treatments for PGAD and their efficacy.

**Methods:** A scoping review was carried out (PRISMA-Scr) that included articles on PGAD as the main disorder, only in women, which explained, in detail, the treatment and its efficacy, was empirical, was written in English and Spanish. No prior filtering by years was performed.

**Outcomes:** Three different effective treatments were found (physical therapies, pharmacological therapies, and psychotherapeutics in combination with other therapies).

**Results:** Thirty-eight articles were selected. From physical therapies, treatments using neuromodulation, transcutaneous electrical stimulation, Botox, surgery, electroconvulsive therapy, manual therapy, pelvic floor therapy, dietary changes, and transcranial magnetic stimulation showed effectiveness. Using the pharmacological approach, paroxetine, duloxetine, pramipexole, ropinirole, and clonazepam treatments were effective. Psychotherapy treatments showed effectiveness only in combination with other types of treatments, specifically a combination of cognitive-behavioral strategies with pharmacological treatment.

**Clinical implications:** Pharmacological treatment, specifically SSRIs, have proven to be the therapy of choice for different subtypes of patients.

**Strengths and limitations:** This study analyzed treatment effectiveness with different approaches and took into consideration those articles where psychotherapy was used as a combination treatment with pharmacological and physical therapy. The main limitation is that it was focused exclusively on women, and the results cannot be generalized to include men.

**Conclusions:** To date, a combination of pharmacological interventions with physical therapy and, in some occasions, with psychological therapy is main strategy followed to accomplish effective treatment of PGAD. **Martín-Vivar M, Villena-Moya A, Mestre-Bach G, et al. Treatments for Persistent Genital Arousal Disorder in Women: A Scoping Review. J Sex Med 2022;19:961–974.**

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**Key Words:** Persistent genital arousal disorder; Female sexual dysfunction; Persistent sexual arousal syndrome; Sexual arousal disorders

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<sup>1</sup>Unidad de Sexología Clínica y Salud Sexual, Consulta Dr. Carlos Chiclana, Madrid, Spain;

<sup>2</sup>Universidad Francisco de Vitoria, Madrid, Spain;

<sup>3</sup>Universidad Internacional de la Rioja, La Rioja, Spain;

<sup>4</sup>Doctor Peset University Hospital, Center for Sexual and Reproductive Health, Valencia, Spain;

<sup>5</sup>University CEU San Pablo, Madrid, Spain

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## INTRODUCTION

### Conceptualization and Prevalence

In recent years, there has been growing scientific interest in persistent genital arousal disorder (PGAD), an uncommon and most likely underdiagnosed disorder.<sup>1</sup> It was first described<sup>2</sup> as a disorder that produces extreme distress, characterized by persistent genital arousal in the form of genital sensations or sensitivity in the genital area in the absence of sexual desire.<sup>3</sup> However, PGAD is not classified in mental health manuals, with the exception of a mention in the latest edition of the International

Classification of Diseases (ICD-11).<sup>4</sup> Consequently, there is no clinical consensus on the diagnosis criteria of PGAD.<sup>3</sup>

The initial criteria proposed by Leiblum and Nathan for this disorder were: (i) Physiological responses characteristic of sexual arousal (genital and breast vasocongestion and sensitivity) that persist for an extended period of time (hours to days); (ii) the signs do not resolve with an ordinary orgasmic experience; (iii) the signs are experienced as unrelated to any subjective sense of sexual excitement or desire; (iv) the signs are experienced as unbidden, intrusive, and unwanted, and an additional criterion is subsequently added, that is, (v) the presence of unwanted genital sensations. These feelings are not resolved by sexual activity.<sup>5</sup> Subsequently, in 2016, the International Society for the Study of Women's Sexual Health (ISSWSH) conceptualized PGAD as a condition “characterized by persistent or recurrent, unwanted or intrusive, distressing feelings of genital arousal or being on the verge of orgasm (genital dysesthesia), not associated with concomitant sexual interest, thoughts, or fantasies for a minimum of 6 months. PGAD can be lifelong or acquired, generalized or situational, and associated with the following characteristics: (i) limited resolution, no resolution, or aggravation of symptoms by sexual activity with or without aversive and/or compromised orgasm in terms of impaired orgasm frequency, intensity, timing, and/or pleasure; (ii) aggravation of genital symptoms by certain circumstances (sitting, car driving, listening to music, general anxiety, stress or nervousness); (iii) despair, emotional lability, catastrophization, and/or suicidality; and (iv) inconsistent evidence of genital arousal on physical examination during symptoms (lubrication, swelling of clitoris or labia).”<sup>5</sup>

Regarding the most frequent symptoms, a survey conducted with 158 women suffering from PGAD found genital symptoms such as tingling of the clitoris (86%), vaginal congestion (80%), vaginal wetness (77%), vaginal contractions (71%), and vaginal tingling (71%). Clitoral pain was reported in 20% of cases.<sup>6</sup>

The prevalence of PGAD is currently unknown due, primarily, to the changing diagnostic criteria and the absence of studies.<sup>3</sup> PGAD is a disorder that was initially diagnosed exclusively in women. A study by the U.K. National Health System suggested a prevalence of approximately 1% of women.<sup>7</sup> Another study in Canada found that 1%–4% of women in a sample of the general population meet the 5 established criteria for PGAD.<sup>3</sup> Furthermore, a number of clinical cases in men have also recently been published.<sup>8–10</sup>

## Factors Associated with PGAD

The etiology of PGAD appears to be complex and multifactorial. A recent review<sup>11</sup> offered several different possibilities: (i) Neurological changes (eg, post-surgery or specific damage to the brain); (ii) peripheral neurological changes (pinching or hypersensitivity of the pelvic nerves); (iii) vascular changes (pelvic congestion); (iv) mechanical pression on the genital structures; (v) changes induced by medication; and (vi) psychological changes

(stress)—or a combination of all the above. In this vein, the ISSWSH considered that the etiology of PGAD should be approached at the biopsychosocial level, given that multiple factors contribute to both the development and maintenance of this disorder. Among these factors, medical (eg, cauda equina pathology and pudendal neuropathy), pharmacological (eg, discontinuation of selective serotonin reuptake inhibitors (SSRIs)), and psychological (eg, catastrophization) aspects were considered, in addition to the few accessible treatment options and the lack of knowledge of clinicians about this disorder.<sup>5</sup>

Medical illnesses are the principal comorbidities detected and reported.<sup>3</sup> Thus, it is essential to conduct a thorough physical examination and review of a patient's medical history in order to rule out local pathologies.<sup>12</sup> Jackowich and Pukall found different comorbidities associated with PGAD: Restless leg syndrome (13.20%), irritable bowel syndrome (9.30%), chronic pelvic pain (7.40%), endometriosis (6.40%), fibromyalgia (6.20%), pelvic floor muscle dysfunction (2.30%), anal pain (1.80%), genital pain (1.20%), and interstitial cystitis (0.80%).<sup>3</sup>

In the described clinical cases, the presence of PGAD appears to be explained exclusively by neurological conditions or alterations such as focal epilepsy<sup>13</sup> or the discontinuing of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) or mood stabilizers.<sup>12,14</sup>

Some studies have detected the existence of morphological factors prior to the development of PGAD.<sup>15</sup> For example, a study of 18 women diagnosed with PGAD found that 12 of them (66.7%) had Tarlov cysts detected with magnetic resonance (MR) imaging, which led to the development of unpleasant genital sensations<sup>16</sup>, and it was subsequently confirmed that Tarlov cysts are associated with PGAD.<sup>17</sup> An association between PGAD in women and other pathologies, such as PGAD and restless leg syndrome, has been also observed.<sup>18</sup>

Additionally, psychological factors have also been shown to be of interest in understanding the course of PGAD. It has been observed that anxiety, along with catastrophic thinking on physical sensations, tends to focus the attention of patients with PGAD on the genital area, leading to greater subjective distress about genital arousal.<sup>19</sup>

A significant relationship has also been detected between anxiety and vaginal pulse amplitude.<sup>3,20</sup> Furthermore, studies have found higher rates of depression, sexual distress, suicidal ideation, and relational disorders than among women without symptoms of PGAD.<sup>3</sup>

Other psychological factors associated with PGAD are the experience of sexual abuse or trauma,<sup>19</sup> personality traits (neuroticism, low openness to experience, and sexual conservatism),<sup>21</sup> obsessive–compulsive symptoms, and somatic anxiety.<sup>22</sup>

## Objectives

Given that PGAD is a pathology that has received little study, the present scoping review aimed to provide an exhaustive

study of the various treatments proposed for PGAD and their effectiveness.

## METHODS

### Eligibility Criteria

The inclusion criteria were: (i) articles dealing specifically with PGAD as the principal disorder; (ii) articles that explain in detail the treatment of PGAD; (iii) studies that evaluate the effectiveness of the treatment; (iv) interventions in women; (v) empirical articles, single cases, series of cases, and randomized clinical trials; and (vi) articles written in Spanish or English.

Excluded articles were those which: (i) did not specifically treat PGAD as the main subject of the article; (ii) did not provide information on the treatment or intervention; (iii) did not provide data on the effectiveness of the treatment with follow-up of the patient after the treatment; (iv) interventions in men; (v) bibliographical reviews, clinical guides, treatment manuals, or books and/or articles; and (vi) articles written in a language other than Spanish or English.

Given the limited number of articles resulting from the search, no initial filter by date was used.

### Information Sources

A search of 2 databases was conducted: PubMed and PsycInfo. The final search took place on January 9, 2021. The references of all of the selected articles were also verified to identify other potentially relevant articles.

### Search

The search terms used were: “Persistent genital arousal disorder” OR “persistent sexual arousal syndrome” OR “restless genital syndrome.”

### Selection of Sources of Evidence

As a first step, all duplicated articles were eliminated. Two independent reviewers (A.V.M. and M.M.V.) analyzed all of the titles and abstracts of the remaining articles. Articles that met the inclusion criteria were analyzed and reviewed in their entirety by both reviewers. Any conflicts in the applied criteria were resolved by consulting a third member of the research team (G.M.B.).

### Data Items

A template was designed to extract the most relevant data from the review. This template included the title of the article, year of publication, name of the first author, objective, type of study, sample size, sample, average patient age, inclusion criteria, outcome measures, treatment, treatment characteristics, follow-up, and results. The data were extracted independently by 2 researchers using the same template. Any conflicts were resolved by consulting a third member of the research team.

## Synthesis of Results

The searches identified a total of 239 articles (147 PubMed; 92 PsycInfo) from the period 2001–2020. Of the total, 66 articles were duplicates and were thus excluded, with 173 articles remaining. An initial screening was made by reviewing titles and abstracts of the articles, discarding 116 articles, with 57 articles remaining for complete reading. After a second screening by reading the entire article, a further 19 were discarded. After this second step, a total of 38 articles met the eligibility criteria and were included in the scoping review. No relevant articles were identified after reviewing the references of the articles found in the initial search.

## Characteristics of the Sources of Evidence

Our scoping review included 38 articles, using which we conducted an in-depth analysis of the different treatments proposed and their effectiveness for PGAD. These 38 studies included a total of 99 female patients with PGAD, and the sample size of each study ranged from 1 to 43 patients. The age range was 16–74 years. Three types of interventions were distinguished: Pharmacological, physical, and psychotherapeutic. Of the studies reviewed, 30 were simple treatments (Table 1): 16 studies were of pharmacological interventions, 13 of physical therapies, 1 of psychotherapy; meanwhile, 8 were of combined treatments (Table 2): 4 articles combined the 3 types of interventions, 2 studies were of pharmacological and psychotherapeutic interventions, and another 2 were of physical and pharmacological treatments. All of them were case studies with 1 or more people attending in the same time-frame.

## RESULTS OF THE INDIVIDUAL SOURCES OF EVIDENCE

### Synthesis of the Results

The results may be classified into 3 broad groups: (i) Physical interventions, (ii) pharmacological interventions, and (iii) psychological interventions.

### Physical Therapies

Treatments based on surgical intervention proved to be the most effective in the remission of symptoms of PGAD. Physical therapies included treatments such as neuromodulation, transcutaneous electrical stimulation (TENS), Botox, surgery, electroconvulsive therapy (ECT), manual therapy, pelvic floor therapy, diet therapy, and transcranial magnetic stimulation (TMS).

**Neuromodulation Treatment.** Chronic pudendal neuromodulation (CPN) consists of electrical stimulation of the nerve with the aim of reducing pelvic floor stimulation. This type of intervention has proven to be effective in reducing the symptoms

**Table 1.** Effectiveness of the simple treatments

Type of therapy	Author, year	N	Study design	Age	Follow-up months	Treatment description	Effectiveness
Physical	Thorne, 2008 <sup>25</sup>	1	Case study— longitudinal	62	1,5	Coil embolization	Treatment of pelvic pain and PGAD symptoms reported by patients were treated by endovascular coil embolization of the ovarian vein. The results showed a clear therapeutic response by remission of symptoms.
	Korda, 2009 <sup>26</sup>	1	Case study— longitudinal	24	48	ECT	After 6 bilateral ECTs, the symptoms disappeared completely. Later, ECT maintenance was needed, as PGAD symptoms relapsed. The frequency was reduced from once every 2 weeks to once every 5 weeks during 42 months. Afterward, the patient reported total remission.
	Rosenbaum, 2010 <sup>29</sup>	1	Case study— longitudinal	27	3,5	Physical therapy and pregnancy garment	The patient was pregnant once the symptoms appeared. A pregnancy garment (Vbrace) to support the vulva and performing daily pelvic floor activity and other habits (avoiding prolonged standing and increased swimming) were recommended. After one week, the symptoms completely disappeared and the patient remained in remission after 14 weeks.
	Waldinger, 2010 <sup>30</sup>	2	Case study— longitudinal	56/61	2	TENS	A 20 min duration of TENS with electrode placed 2 cm medial to the tuber ischiadicum, patients reported 80% remission. Afterward, for 2 months, 30 min TENS used 6 times per day provided maximal reduction (90%). Both patients showed similar results following this treatment strategy.
	Nazik, 2014 <sup>34</sup>	2	Case study— longitudinal	23/38	8	Botulinum toxin injection	<i>Clostridium botulinum</i> toxin type A were applied in the periclitoral region in order to block the dorsal nerve of the clitoris. A total of 4 units/0.1 mL was applied. Both patients reported significant remission of symptoms, but no complete remission.
	Feigenbaum, 2015 <sup>17</sup>	11	Case study— longitudinal	m.a. 46	23	Sacral laminectomy	Sacral laminectomy was carried out to expose symptomatic cysts. The surgical strategy varied depending on the cyst type involved. In all cases reported, the final goal was spinal nerve root decompression. After surgery, 7 patients reported complete elimination, three reported significant remission, and 1 reported no changes in their PGAD symptoms.
	Armstrong, 2016 <sup>37</sup>	1	Case study— longitudinal	35	6	Sacral neuromodulation	Surgery in the form of bilateral pudendal nerve released with neuromodulator insertion (4 lead neurostimulator—2 leads at the sacral hiatus and 2 adjacent to the pudendal nerves). After 6 months, almost total remission of PGAD symptoms occurred, except for emergency urinary sensations.
	Jones, 2016 <sup>40</sup>	1	Case study— longitudinal	32	24	Sacral neuromodulation	Traditional 2 stage procedure with left-sided unilateral S3 lead placement was performed. The S3 placement was confirmed intraoperatively with a demonstration of dorsiflexion. In the first week, the patient reported 50% symptom reduction. Two years after treatment, they still reported significant improvement regarding PGAD symptoms

(continued)

Table 1. Continued

Type of therapy	Author, year	N	Study design	Age	Follow-up months	Treatment description	Effectiveness
	McMullen, 2016 <sup>41</sup>	1	Case study—longitudinal	29	5	Transcranial magnetic stimulation	Inhibitory TMS bilaterally on the motor strip in the pelvis area on the homunculus was performed (2000 pulses at 1 Hz). After 9 treatments, the treatment was changed to continuous theta burst stimulation (cTBS). After 3 months, the patient reported complete remission, maintained until the follow-up 2 months later.
	Cohen, 2017 <sup>42</sup>	1	Case study—longitudinal	40	3	Botulinum toxin injection	Bilateral pudendal nerve block followed by subsequent intravaginal onabotulinumtoxinA injection were performed. After 30 min following the injection, the patient reported more than a 50% symptom reduction. Two weeks later, an injection of corticosteroid triamcinolone was performed, also maintaining more than 50% symptom reduction. Follow-up in the third month confirmed a significant reduction in PGAD symptoms
	Gaines, 2018 <sup>43</sup>	6	Case study—longitudinal	m.a. 52	26	Chronic pudendal neuromodulation	A quadripolar tine lead was placed at the pudendal nerve using the ischial–rectal approach. The lead was tested across 2 weeks, obtaining a 50% symptom reduction; then, all patients were moved to stage II of implantation. Five of the 6 reported more than a 50% remission 26 months later.
	Klifto, 2020 <sup>47</sup>	8	Case study—longitudinal	m.a. 51	2,5	Neurolysis pudendal nerve	Decompression (neurolysis) of the dorsal branch of the pudendal nerve was performed. All patients reported moderate-to-significant remission of symptoms a few days later. The follow-up reported small remission of PGAD symptoms.
Pharmacological	Wylie, 2006 <sup>24</sup>	1	Case study—longitudinal	66	4	Paroxetine and risperidone	Trial of clomipramine (10 mg) was first applied. Then, it changed to 10 mg of paroxetine, with 25% improvement in PGAD symptoms. This was not sustained even at higher doses. Risperidone (2 mg/day across 4 weeks) was prescribed and resulted in a partial reduction in symptoms.
	Korda, 2009 <sup>27</sup>	1	Case study—longitudinal	49	12	Varenicline	Several pharmacologic agents were tested (morphine, enalapril, and valsartan) with a temporary reduction in symptoms. Varenicline was prescribed as part of the patient's decision to quit smoking. After 2 weeks, the patient reported complete remission of symptoms. This was confirmed after 12 months of follow-up.
	Waldinger, 2009 <sup>18</sup>	18	Case study—longitudinal	m.a. 53	Multiple	Clonazepam, estradiol, pramipexol, tramadol, and oxazepam	Clonazepam ameliorated PGAD symptoms (60%–90%) in 25% of the women. Additionally, oxazepam resulted in a similar efficiency. Estradiol (2 mg/day) also reduced PGAD symptoms in 1 patient. Pramipexol (50 mg) was not efficient, and tramadol was effective (60%–100%) only while it was present in the body. After 4 h, all patients reported PGAD symptoms.

(continued)

Table 1. Continued

Type of therapy	Author, year	N	Study design	Age	Follow-up months	Treatment description	Effectiveness
	Anzelloti, 2010 <sup>28</sup>	1	Case study— longitudinal	40	6	Topiramate	Topiramate treatment (300 mg/day) was prescribed as part of antiepileptic chronic therapy. The patient reported significant remission of symptoms and showed potential neural improvement in epileptic dysfunction.
	Philippsohn, 2012 <sup>31</sup>	2	Case study— longitudinal	36/41	13	Duloxetine	Serotonin and norepinephrine reuptake inhibitors (duloxetine) were chosen for treatment, starting at 30 mg and increased to 60 mg per day. In 1 week, the patients reported partial remission of symptoms. In 4 months, both patients reported full remission, confirmed at the 13-month follow-up.
	Gadit, 2013 <sup>32</sup>	1	Case study— longitudinal	54	3	Citalopram, clonazepam, and zopiclone	Citalopram (20 mg/day), clonazepam (0.5 mg/twice daily), and zopiclone (7.5 mg/night) were prescribed. No improvement in PGAD symptoms was reported by the patient.
	De Magalhaes, 2015 <sup>35</sup>	1	Case study— longitudinal	57	4	Paroxetine and lorazepam	Lorazepam (1 mg/day) and paroxetine (30 mg/day) were prescribed. After a few weeks of treatment, the patient reported partial remission of PGAD symptoms.
	Deka, 2015 <sup>36</sup>	1	Case study— longitudinal	53	18	Leuprolide	Initial treatment consisted of clomipramine (150 mg/day) and clonazepam (1.5 mg/day). After 2 weeks, it was changed to fluoxetine (40 mg/day) without any success. Afterward, an antiandrogen (leuprolide, 3.75 mg) was injected subcutaneously. A few days after, the patient reported significant remission. After a third injection, and at the 18-month follow-up, the patient report no PGAD symptoms.
	Camkurt, 2017 <sup>38</sup>	1	Case study— longitudinal	36	9	Paroxetine	Paroxetine (20 mg/day) was prescribed. One week later, the patient reported mild remission of PGAD symptoms. Treatment was increased up to 60 mg/day across 6 weeks; after this and 9 months after the initial application, the patient was stable in terms of PGAD symptoms.
	Fountoulakis, 2017 <sup>39</sup>	1	Case study— longitudinal	62	24	Haloperidol and paliperidone	Haloperidol (10 mg/day) was prescribed and the patient reported a significant reduction in symptoms. Treatment was changed to paliperidone (18 mg/day) in search of better side effects. The patient reported approximately 50% symptom remission. After 2 years, the symptoms were stable.
	Sforza, 2017 <sup>44</sup>	1	Case study— longitudinal	74	24	Pramipexole	Pramipexol (0.25mg/day, 1–2 h before going to sleep) was prescribed. The patient reported a reduction in the frequency and intensity of genital discomfort.
	Yildirim, 2017 <sup>45</sup>	7	Case study— longitudinal	25-70	24	Clomipramine	Clomipramine (75 mg/day, increased to 150 mg/day) was prescribed. The patients reported an effective improvement in symptoms with a long-lasting effect.
	Ahmad, 2018 <sup>8</sup>	2		50/72	48		
		1	Case study— longitudinal	44	3	Ropinirole	The patient was prescribed pharmacologic treatment to influence the dopaminergic mechanism. For this purpose, ropinirole (0.5 mg/day, increased to 1 mg/day) was applied, which proved to be effective in PGAD remission.

(continued)

Table 1. Continued

Type of therapy	Author, year	N	Study design	Age	Follow-up months	Treatment description	Effectiveness
	Gunduz, 2019 <sup>46</sup>	1	Case study—longitudinal	42	1,5	Duloxetine and diazepam	A patient with psychiatric attention was prescribed duloxetine (30 mg) to reduce PGAD symptoms, as well as diazepam (5 mg/day) to clear depressive complaints. Two weeks later, duloxetine was increased to 60 mg and diazepam was stopped. PGAD symptoms after the first month regressed by 80%. After 45 days, the patient reported significant remission of symptoms.
	Dallagiocoma, 2020 <sup>48</sup>	1	Case study—longitudinal	31	-	Duloxetine	Duloxetine (no dose confirmed) was prescribed to a psychiatric patient with depression and anxiety comorbidities. Partial remission of symptoms was reported.
Psychotherapy	Elkins, 2014 <sup>33</sup>	1	Case study—longitudinal	71	-	Hypnotherapy	Nine sessions of hypnosis for a pre-qualified patient suffering PGAD symptoms were conducted. All sessions were 45 min in duration, biweekly. The patient reported no changes in PGAD symptoms at worst, but a significant improvement in symptoms at best.

m.a. = mean age; N = sample size; SSRIs = selective serotonin reuptake inhibitors; SNM = sacral neuromodulation; TENS = transcutaneous electrical nerve stimulation; TMS = transcranial magnetic stimulation.

of PGAD by regulating afferent signals.<sup>43</sup> In the same line, applying the neuromodulation of the sacral nerve (SNM) has proven effective.<sup>37,40</sup>

**TENS.** The TENS technique consists of the application of electrical stimuli to reduce overstimulation in a specific area. The procedure consists of an initial test phase conducted with professionals, where, for 20 minutes, the patient activates the device to see if the PGAD symptoms decrease. The patient is then instructed on how to use the device independently at home.<sup>30</sup> The authors applied this treatment to 2 patients, recommending a frequency of 110 Hz for a period of 80 minutes every day for 2 months. The patients showed a remission of 80%–91% of the symptomatology throughout the regular follow-up visits after treatment.

**Physical Therapy with OnabotulinumtoxinA (Botox).**

The application of Botox seeks to reduce the nociceptive sensitivity of patients. In a study, effective results were found with the application of Botox<sup>34</sup> alone, as well as treatment with lidocaine (0.25%, 10 mL) in the pudendal nerve and a subsequent injection of Botox.<sup>42</sup> In this same study, treatment with lidocaine and/or Botox was compared with escitalopram, pregabalin, and acupuncture, proving that the first treatment was more effective. The same results were found by 1 recent study<sup>56</sup>, where this treatment was applied without any remission of the symptoms of PGAD.

**Surgery Treatments.** One of the most effective surgical treatments for PGAD is neurolysis of the dorsal branch of the pudendal nerve.<sup>47</sup> This procedure consists of producing a decompression or liberation of the dorsal brand of the pudendal nerve of the patient using anesthesia and a bipolar coagulant with the lowest voltage possible. In the study, 7 of the 8 women reported complete remission of arousal symptoms and the recovery of the ability to have habitual sexual relations.<sup>47</sup>

Taking into account that PGAD may be associated with the appearance of cysts in the genital area,<sup>16</sup> another treatment that has proven effective is “sacral laminectomy.”<sup>17</sup> In this case, although Tarlov cysts were more numerous, the surgical strategy to treat meningeal cysts varied according to the type of cyst, but in all cases, the aim of the surgery was the decompression of the root of the spinal nerve. In the reported case, in 91% of cases, the symptoms of PGAD improved or were eliminated entirely after surgical decompression of the cyst.

Finally, moderate-to-low levels of effectiveness were reported in the treatment by a clitoridectomy combined with pharmacological treatment.<sup>30</sup> There was only a partial reduction in spontaneous orgasms without a complete remission of the other symptoms, leading to the authors doubting the effectiveness of the treatment.

Table 2. Combined treatments

Type of combined therapy	Author, year	N	Study design	Age	Follow-up months	Treatment description	Effectiveness
Pharmacology and psychotherapy	Hiller, 2007 <sup>50</sup>	1	Longitudinal—case study	52	-	Amitriptyline (50 mg/thrice daily), cognitive—behavioral therapy, and couple therapy	Psychotherapy was conducted to perform psychoeducation about the causes and symptoms of PGAD related to effectiveness in improving the management of masturbatory needs and reducing anxiety, shame, and blame. A couple of sessions, to set up arrangements regarding sexual interactions, helped to achieve better emotional and sexual responses, decreased on couple tension. Pharmacological treatment consisted of amitriptyline, which improves sleep patterns, but no improvement was reported in PGAD symptoms.
	Aswath, 2016 <sup>53</sup>	1	Longitudinal—case study	40	2	Carbamazepine and psychotherapy sessions	Carbamazepine treatment (600 mg/day) did not show any reduction in PGAD symptoms, so the patient stopped taking it after 1 month. Supportive sessions about PGAD symptoms were conducted for two months. The patient reported a reduction in the frequency and intensity of symptoms and showed an asymptomatic status after two months.
	Hrynko, 2017 <sup>54</sup>	1	Longitudinal—case study	40	-	Venlafaxine, sertraline, alprazolam, escitalopram, doxepin, cognitive—behavioral therapy, and systemic therapy	The patient was preliminarily diagnosed with a neurotic disorder. Several pharmacological attempts of treatment were tried: Venlafaxine (150 mg/day), sertraline (200 mg/day), alprazolam (1 mg/day), doxepin (100 mg/day), and escitalopram (10 mg/day). None of them showed significant improvement PGAD symptoms, so the patient refused further pharmacological treatment. Systemic therapy, relaxation techniques, and cognitive and experience-based techniques from cognitive—behavioral therapy were used. This treatment resulted in a gradual reduction in tension and an alleviation of most of the symptoms.
	Curran, 2019 <sup>55</sup>	1	Longitudinal—case study	16	8	Bupropion (150 mg/day), SSRIs, and trauma-focused counseling	A patient with a history of depression, sexual abuse, and morbid obesity underwent bupropion (150 mg/day) and SSRI treatment (not specified). She reported PGAD symptoms after she initiated hormonal contraception with a vaginal ring (etonogestrel rod). At the beginning, SSRIs were stopped and the vaginal ring implant was removed. Treatment consisted of restarting SSRIs, reinitiating hormonal conception with a vaginal ring, and starting trauma-focused counseling with a psychotherapist. After 8 months of symptoms, she decided to remove the vaginal ring implant and carried on taking SSRIs. Unwanted persistent arousal and spontaneous orgasm were resolved.
	Physical intervention and pharmacology	Yero, 2006 <sup>49</sup>	2	Longitudinal—case study	52/28	9	ECT and valproic acid
Waldinger, 2010 <sup>51</sup>		1	Longitudinal—case study	77	-	Clonazepam, 0.5% bupivacaine hydrochloride monohydrate, and clitoridectomy	The patient reported an increase in PGAD symptoms with no clear origin. The first treatment was physical intervention by completely resecting the clitoris and crura. After this, spontaneous orgasms did not recur post-surgery, but dysesthesia, paresthesia, and feelings of imminent orgasm remained persistent. Pharmacological treatment was initiated with clonazepam, but with transient and limited effect. Local injections were performed in order to try to investigate the effect of local anesthetizing infiltration (1 cc of 0.5% bupivacaine hydrochloride monohydrate) on the left pudendal nerve. This intervention was effective for 72 h, but by day, 4 all symptoms had recurred.

(continued)



Table 2. Continued

Type of combined therapy	Author, year	N	Study design	Age	Follow-up months	Treatment description	Effectiveness
Physical intervention, pharmacology, and psychotherapy	Eibye, 2014 <sup>52</sup>	1	Longitudinal—case study	31	78	Mindfulness, paroxetine, mirtazapine, and ECT	The patient initiated treatment with physiotherapy, but the exercises only improved the symptoms briefly. Anxiolytic and sleep medications (benzodiazepine, triazolam, melatonin, and zopiclone) were initiated, but did not provide the patient any relief. Tramadol and mirtazapine were also used with no success. Five sessions of ECT were conducted, completely resolving the symptoms, but the patient refused to remain on the treatment and symptoms slowly relapsed. Individual psychotherapy sessions, together with an intensive psychiatric ward for rightful medical administration, was conducted without obtaining complete remission of symptoms.
	Oaklander, 2020 <sup>56</sup>	11	Longitudinal—case study	m.a. 53.4	-	Gynecological and urological treatment, duloxetine, immunoglobulins, psychiatric treatment, and hospitalization	Psychiatric treatment showed no effect; gynecological and urological treatments were also ineffective. Neurological treatment was effective in 80% of the patients, dramatically improving patient 8's PGAD and motor symptoms. Botox for 1 patient was ineffective.
	Amsterdam 2005 <sup>23</sup>	1	Longitudinal—case study	44	3	Dietary modification and supportive counseling	The patient declined any surgical or medical treatment. A reduction in soy intake (excessive) and supportive counseling with a therapist were performed. PGAD symptoms and menstrual complaints were completely resolved.

CBT = cognitive-behavioral therapy; ECT = electroconvulsive therapy; m.a. = mean age; N = sample size; PGAD = persistent genital arousal disorder; SSRIs = selective serotonin reuptake inhibitors.

**Electroconvulsive Therapy (ECT).** This technique involves the application of an electrical current to the brain, causing brief and intentional convulsions in the patient. The treatment consists of various sessions with different intensities, depending on the results obtained.<sup>27</sup>

This treatment has been proven effective for clinical patients with type 1 bipolar disorder.<sup>27,49</sup> In the most recently reported case, the treatment consisted of 30 sessions to achieve a remission of the symptoms of PGAD. Minimal side effects were reported (short-term memory loss, headaches, and muscle pain).<sup>27</sup>

This type of intervention has also been found effective in combination with pharmacotherapy and psychotherapy in patients with possible comorbidities (in this case, anxiety and depression). The results were reported as effective and the combination reduced the final number of required sessions of ECT to 5.<sup>52</sup>

Despite the potential benefits of ECT in some patients resistant to other treatments, it is important to note that the research to date is limited, where ECT is never the first-line treatment option and it has only been used in cases with comorbidities of mood disorders and suicide attempts with refractory PGAD.<sup>27</sup>

**Other Interventions.** Other interventions proposed for the treatment of PGAD were: (i) Manual therapy of soft tissue and relieving the tension in the internal obturator muscle<sup>29</sup>; (ii) treatment of pelvic floor pain with ovarian vein coil embolization<sup>25</sup>; (iii) diet low in phytoestrogens<sup>23</sup>; and (iv) transcranial magnetic stimulation.<sup>41</sup>

**Pharmacological Treatment**

A total of 17 articles were found to report entirely pharmacological interventions, and a further 8 articles where this was combined with other treatments. Pharmacological treatments were the most frequent and most studied in the publications investigated in this scoping review compared to physical therapies and psychological interventions.

**Antidepressants.** Within the family of selective serotonin reuptake inhibitors (SSRIs), paroxetine is a drug that has been the most studied for its use for PGAD. Various studies have shown that a daily dose of between 20 and 30 mg of paroxetine can be effective in reducing the symptoms of PGAD, especially in the occurrence of spontaneous orgasms.<sup>38</sup> Other studies have not found complete remission, but have observed a partial reduction in the symptoms of PGAD.<sup>24,35</sup> There have also been cases reported in which the treatment of the symptoms of PGAD with paroxetine have been entirely ineffective.<sup>52</sup>

Duloxetine is another drug that has been used and reported as effective. In addition to being effective in the reduction of the symptoms of arousal, masturbation, and genital pain,<sup>46,56</sup> it is also effective in reducing the comorbid symptoms of anxiety and

depression.<sup>46</sup> Treatment with this drug has also been effective in the partial reduction of the symptoms of PGAD in a woman with Tarlov cysts.<sup>48</sup> By contrast, a recent study found that only 2 of 11 cases of treatment with duloxetine was it effective in reducing the symptoms of PGAD.<sup>56</sup>

Another pharmacological treatment uses a combination of different antidepressants and other drugs. For example, the combination of clomipramine (150 mg/day) and fluoxetine (40 mg/day), along with anxiolytics (clonazepam) and a subsequent injection of leuprolide, resulted in a notable improvement in symptoms.<sup>36</sup> Treatment with clomipramine alone (75–150 mg/day) also proved effective in the remission of symptoms, especially arousal.<sup>45</sup>

Studies have reported that treatments using other drugs such as venlafaxine (150 mg/day), sertraline (200 mg/day), and escitalopram (10 mg/day)<sup>54</sup> or citalopram (20 mg/day) showed no significant benefits.<sup>32</sup>

**Anxiolytics.** A number of studies have found clonazepam to be effective in the reduction of symptoms of PGAD.<sup>18,36</sup> However, in subsequent studies, zopiclone (7.5 mg) was combined with clonazepam (0.5 mg)<sup>32</sup> and mirtazapine<sup>52</sup> without observing any type of reduction in the symptoms of PGAD.

**Drugs with Dopaminergic Action.** Treatment with pramipexole (0.25 mg, administered 1–2 h before sleep) was shown to result in a reduction in the frequency and intensity of genital discomfort after 2 weeks of treatment in a women 74 years of age.<sup>44</sup> Treatment with ropinirole 0.5 mg/daily, later increased to twice a day and finally 1 mg in the morning and 0.5 mg at night, also proved to be effective.<sup>8</sup> This supports the theory that the pathophysiology of PGAD involves dopaminergic mechanisms.

**Other Drugs.** Carbamazepine (600 mg/day) is 1 of the drugs also used to treat the symptoms of PGAD. The reported effectiveness is limited, partly due to discontinuous use of the drug during treatment on the part of the patient.<sup>53</sup> Another drug that has been shown to be effective is bupropion.<sup>55</sup> In this case, the drug was combined with psychological therapy as the patient presented the comorbidities of depression and trauma after suffering sexual abuse.

## Psychological Interventions

Only 1 study was found to rely exclusively on psychotherapy, and 6 studies where psychotherapy was used in combination with other forms of intervention were found.

In 2 of these studies, therapeutic support and alliance were used. Therapists provide a safe space to resolve doubts and to allow the patient to feel supported and accompanied during the procedure.<sup>53,54</sup> In these studies, the effectiveness of the treatment and the remission of symptoms appears to be associated with

therapeutic support, but they do not offer standardized measures to demonstrate their effectiveness or a contrast of the results with other forms of intervention.

Cognitive–behavior therapy (CBT) has also been used in several cases, specifically using distraction techniques, relaxation exercises, and psychoeducation. These techniques have also been used to manage patients' symptoms of anxiety, guilt, and shame associated with PGAD<sup>50</sup> and as relaxation strategies.<sup>54</sup>

Other reported therapies include couples therapy to deal with problems associated with the symptoms of PGAD and their impact on conjugal life.<sup>50</sup> Factors such as establishing limits, expressing emotions, and developing strategies for the self-resolution of problems enhance the wellbeing of the patient. In cases of comorbidities of trauma, it has been shown that applying strategies to address trauma while treating PGAD are effective in reducing the symptoms of anxiety or depression.<sup>55</sup> Another technique that is effective in improving patient wellbeing is mindfulness.<sup>52</sup>

The majority of articles using psychological intervention did so in combination with pharmacological treatment.<sup>50,52–56</sup> This combination appears to be effective in dealing with the course of treatment until the total or partial remission of symptoms of PGAD.<sup>54</sup>

Hypnotherapy is the only treatment that has proven effective without any other type of treatment. It has been shown effective in a single case with psychological intervention (hypnotherapy). The patient underwent eye fixation hypnosis induction over the course of 9 biweekly sessions of 45 minutes to analyze the symptoms and the impact of PGAD on different aspects of the patient's life. The patient, 71 years of age, reported a considerable improvement in the symptomology associated with PGAD.<sup>33</sup>

## DISCUSSION

In this scoping review, we identified 38 primary studies addressing the effectiveness of the different effective interventions for PGAD published between 2001 and 2020. Given that the criteria of this disorder have only recently been established and agreed, a wide range of types of treatments were found. Nevertheless, there is still a debate about the conceptualization, etiology, and types of interventions.

In recent years, there has been increasing evidence on the influence of morphological factors in relation to the etiology of PGAD.<sup>15</sup> In particular, Taylor cysts stand out as a possible explanation for the development of PGAD symptoms, which may be present in up to 66.7%<sup>16</sup> of patients. Therefore, physical treatments seem to have an important weight according to the most recent<sup>16,17</sup> research.

Even so, over the years, pharmacological treatment has been the most widely used in case studies, but with contradictory results using the same drugs. Psychological intervention has been

the treatment least taken into account, or used in a complementary or combined form.

Nevertheless, we found different gaps in the literature, such as in the study designs, most of them being single cases, the lack of specification of evaluation protocols, or the heterogeneity of the intervention protocols.

Considering these nuances, in our study, we identified 3 intervention groups that have demonstrated efficacy. These may be classified into 3 broad groups: (i) Pharmacological, (ii) physical, and (iii) psychological.

Pharmacological therapy appears to be the most studied interventions to date for treating PGAD symptoms in many studies, most of them showing effectiveness in alleviating the symptoms of PGAD.<sup>36,46,56</sup> However, each study used different drugs and doses, making it difficult to determine which drug may be most effective and which are the mechanisms underlying their effectiveness. Furthermore, contradictory results were also found; for example, in the case of SSRIs, some authors<sup>46,56</sup> were able to demonstrate their effectiveness, while others did not find effective results.<sup>52,54</sup>

Physical therapies also appear to be particularly effective in the treatment of PGAD. The proposed interventions (TENS, ECT, SNM, surgery, Botox, and CPN) are novel for this type of pathology and therefore require further research and analysis in order to address the structural etiology of PGAD in certain patients.<sup>30,37,42,43,52</sup> In this regard, different techniques are performed in a very heterogeneous way and in patients with very different morphological and psychopathological characteristics, making it difficult to make the results applicable to the wide range of patients suffering from PGAD.

Although based solely on the results of a single intervention, the results of psychological therapy appear to indicate that patients can benefit from psychotherapeutic accompaniment, both individually and in combination.<sup>50,54–56</sup> These results may be due to psychosomatic factors or associated stigma and symptoms (anxiety, depression, and obsessions), which may coexist with PGAD.<sup>3,22</sup> In the absence of more comparative studies, it is difficult to determine the factors associated with effective interventions.

## Limitations

The studies included in the present review had the following limitations:

1. Given the lack of a specific clinical diagnosis for PGAD and the absence of tools to facilitate a diagnosis of this pathology, it is highly probable that the studies included in the review made use of heterogeneous diagnostic criteria in the diagnosis of patients.
2. Most of the studies on PGAD treatment were case studies, most likely due to the limited prevalence of the disorder. A study of a single case does not allow for a control group to contrast the real effectiveness of each intervention. Thus, the results of the studies must be interpreted with caution.

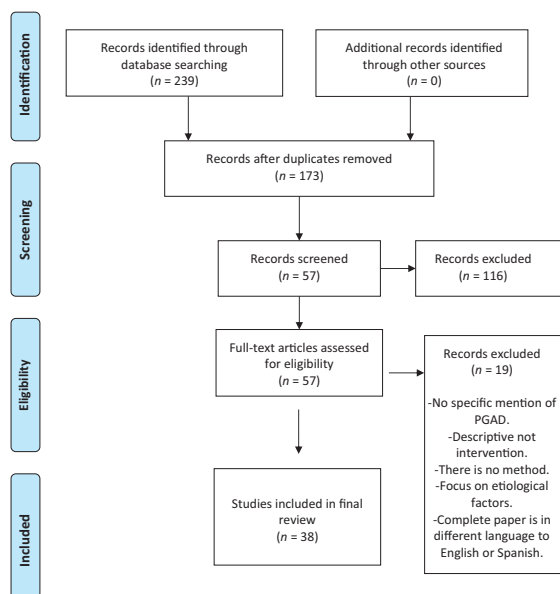


Figure 1. Data charting.

3. A comparison of the results of different studies is virtually impossible, given the heterogeneity of the treatments employed by different authors.

Regarding the scoping review, it should be noted that, to the best of our knowledge, this is the first review of the various treatments proposed for PGAD. Thus, this may serve to provide greater awareness of this pathology and encourage new lines of research into treatment. However, the review itself is not without limitations, the principal being that it is focused exclusively on women and the results cannot be generalized to include men. Furthermore, this review made use of only 2 databases, which may have limited the total number of articles included (Figure 1).

## CONCLUSIONS

There are several effective interventions in treating PGAD. To date, pharmacological interventions, specifically SSRIs, are the treatment of choice and the most studied in the literature. Nevertheless, the different morphological etiologies suggest the importance of physical treatments and an adaptation to each patient, to choose 1 type of treatment or the combination of both. Psychological therapies can also be combined with the other interventions in a complementary way when the background of the patients so requires. However, the treatment of PGAD remains open to scientific debate, and further research is necessary to provide more effective treatment to patients suffering from this symptomatology.

This review revealed the need to create standardized protocols and clinical guides for the adequate evaluation of patients seeking help for the symptoms of PGAD, as well as to identify effective intervention techniques. It is necessary to reach a consensus within the scientific and medical community on the different

patient profiles to establish an adequate guide for decision making to help patients in reducing the symptoms of PGAD. The development of an international template is also recommended for the collection of clinical information to accumulate evidence and conduct research.

It is also recommended to establish a differentiated classification of patients according to their etiology; determining if the etiology is neurological, morphological, associated medical illnesses, discontinuance of pharmaceutical treatment, comorbid psychiatric disorders, or psychosomatic to evaluate the effectiveness of different treatments on different clinical profiles.

**Corresponding Author:** Gemma Mestre-Bach, PhD, Universidad Internacional de la Rioja, La Rioja Spain; E-mail: [gemma.mestre@unir.net](mailto:gemma.mestre@unir.net)

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## STATEMENT OF AUTHORSHIP

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